0300. The SignalP predicts a likely cleavage site for a NOV21c peptide between amino acid positions 14 and 15, *i.e.* at the sequence SEG-VT.

On page 169, please replace Table 21G with the following:

a2

Table 21G. Encoded NOV21c Protein Sequence (SEQ ID NO:68)
MSVKPSWGPGPSEGVTAVPTSDLGEIHNWTELLDLFNHTLSECHVELSQSTKRVVLFALYLAMFVVGLVENLLVI CVNWRGSGRAGLMNLYILNMAIADLGIVLSLPVWMLEVTLDYTWLWGSFSCRFTHYFYFVNMYSSIFFLLPFPLI TVFNVLTACRLRQPGQPKSRRHCLLLCAYVAVFVMCWLPYHVTLLLLTLHGTHISLHCHLVHLLYFFYDVIDCFS MLHCVINPILYNFLSPHFRGRLLNAVVHYLPKDQTKGGHMRLLFLLFHPAFHHHHQGDSQPAAAAPHPEPSLSFQ AHHLLPNTSPISPTQPLTPS

REMARKS

Applicants submit a Sequence Listing for the nucleotide sequences and amino acid sequences disclosed in the specification in compliance with the requirements for patent applications containing nucleotide sequences and/or amino acid sequence disclosures. 37 C.F.R. §§ 1.821-1.825.

By this Amendment, Applicants have also amended the specification to correct a typographical error on page 163 where the second reference to SEQ ID NO:300 should be to SEQ ID NO:301, as SEQ ID NO:300 has been previously assigned to another sequence. Applicants have also amended the specification to correct two typographical errors on page 169, line 4 and page 169 in Table 21G. In both cases it should read SEQ ID NO:68 not SEQ ID NO:58 as SEQ ID NO:58 has been previously assigned to another sequence. No new matter is added. A version marked to show changes of page 163 and 169 of the specification is enclosed with this Amendment.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding this amendment and remark, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

DATE: October 11, 2002

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Eric Sinn, Reg. No. 40,177
Attorneys for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

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Version With Markings To Show Changes

```
NOV20:  251  CCRYPLTVDFEAFGWD-WIIAPKRYKANYCSGQCEYMFMQKYPHTH------LVQQANPR  303
             | |+ | |||+  ||| ||||||  | | || |+| +   ++   |+      ||   +|
Sbjct:  1    CRRHDLYVDFKDLGWDDWIIAPKGYNAYYCEGECPFPLSERLNATNHAIVQSLVHALDPG  60

NOV20:  304  GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS  345  (SEQ ID NO:299X)
                 ||| |||+||++|||++|   ++    | |||+ |||
Sbjct:  61   AVPKPCCVPTKLSPLSMLYYDDDGNVVLRNYPNMVVEECGCR  102  (SEQ ID NO:300)


gnl|Pfam|pfam00019, TGF-beta, Transforming growth factor beta like domain.
             CD-Length = 105 residues,  97.1% aligned
             Score =  103 bits (256), Expect = 2e-23
NOV20:  251  CCRYPLTVDFEAFGW-DWIIAPKRYKANYCSGQCEYMFMQKYPHTH------LVQQANPR  303
             |    | |||   || ||||||+ | |||||| | +        ++      ||+  |||
Sbjct:  4    CRLRSLYVDFRDLGWGDWIIAPEGYIANYCSGSCPFPLRDDLNLSNHAILQTLVRLRNPR  63

NOV20:  304  GSAGPCCTPTKMSPINMLYFNDKQQIIYGKIPGMVVDRCGCS  345  (SEQ ID NO:299)
                 ||| |||+||++|||+|   ++    | | |  |||
Sbjct:  64   AVPQPCCVPTKLSPLSMLYLDDNSNVVLRLYPNMSVKECGCR  105  (SEQ ID NO:30[0]1)


gnl|Pfam|pfam00688, TGFb_propeptide, TGF-beta propeptide. This propeptide is known as
latency associated peptide (LAP) in TGF-beta. LAP is a homodimer which is disulfide linked
to TGF-beta binding protein.
             CD-Length = 227 residues,  46.3% aligned
             Score = 48.1 bits (113), Expect = 8e-07
(SEQ ID NO:302)
NOV20:  62   CPVCVWRQHSRELRLESIKSQILSKLRLKEAPNISREVVKQLLPKAPPLQQILDLHDFQG  121
             |     |+  ++ |||+|+ ||||||  |+  |  |+|            + +|||++
Sbjct:  1    CRPLDLRRSQKQDRLEAIEGQILSKLGLRRRPRPSKE-------PMVVPEYMLDLYNALS  53

NOV20: 122   DALQ--PEDFLEEDEYHATTETVISMAQ-----ETDPAVQTDGSPLCCHFHF 166
             +  +        |  +|         +  +      |+|    ++         | |
Sbjct: 54    ELEEGKVGRVPEISDYDGREAGRANTIRSFSHLESDDFEESTPESHRKRFRF 105
(SEQ ID NO:303)
```

The homology and domain information indicate that the sequence of the invention has properties similar to those of other proteins known to contain this/these domain(s) and similar to the properties of these domains.

Transforming growth factor-beta (TGF-beta) is a multifunctional peptide that controls proliferation, differentiation and other functions in many cell types. TGF-beta-1 is a peptide of 112 amino acid residues derived by proteolytic cleavage from the C-terminal of a precursor protein. See IPR001839.

A number of proteins are known to be related to TGF-beta-1. Proteins from the TGF-beta family are only active as homo- or heterodimer; the two chains being linked by a single disulfide bond. From X-ray studies of TGF-beta-2, it is known that all the other cysteines are involved in intrachain disulfide bonds. As shown in the following schematic representation, there are four disulfide bonds in the TGF-betas and in inhibin beta chains, while the other members of this family lack the first bond.

Version With Markings To Show Changes

The disclosed NOV21c nucleic acid sequence maps to chromosome 12 and has 549 of 559 bases (98%) identical to a gb:GENBANK-ID:AR012140|acc:AR012140.1 mRNA from Unknown. (Sequence 1 from patent US 5763218) ($E = 9.3e^{-115}$).

A disclosed NOV21c polypeptide (SEQ ID NO:[5]68) is 320 amino acid residues in length and is presented using the one-letter amino acid code in Table 21G. The SignalP, Psort and/or Hydropathy results predict that NOV21c has a signal peptide and is likely to be localized to the plasma membrane with a certainty of 0.6000. In alternative embodiments, a NOV21c polypeptide is located to the Golgi body with a certainty of 0.4000, the endoplasmic reticulum (membrane) with a certainty of 0.3000, or the mitochondrial inner membrane with a certainty of 0300. The SignalP predicts a likely cleavage site for a NOV21c peptide between amino acid positions 14 and 15, *i.e.* at the sequence SEG-VT.

Table 21G. Encoded NOV21c Protein Sequence (SEQ ID NO:[5]68)

```
MSVKPSWGPGPSEGVTAVPTSDLGEIHNWTELLDLFNHTLSECHVELSQSTKRVVLFALYLAMFVVGLVENLLVI
CVNWRGSGRAGLMNLYILNMAIADLGIVLSLPVWMLEVTLDYTWLWGSFSCRFTHYFYFVNMYSSIFFLLPFPLI
TVFNVLTACRLRQPGQPKSRRHCLLLCAYVAVFVMCWLPYHVTLLLLTLHGTHISLHCHLVHLLYFFYDVIDCFS
MLHCVINPILYNFLSPHFRGRLLNAVVHYLPKDQTKGGHMRLLFLLFHPAFHHHHQGDSQPAAAAPHPEPSLSFQ
AHHLLPNTSPISPTQPLTPS
```

The NOV21c amino acid sequence was found to have 159 of 178 amino acid residues (89%) identical to, and 160 of 178 amino acid residues (89%) similar to, the 404 amino acid residue ptnr:SWISSNEW-ACC:O15218 protein from Homo sapiens (Human) (ADRENOMEDULLIN RECEPTOR (AM-R)) ($E = 7.1e^{-84}$).

NOV21c is expressed in at least the following tissues: heart, skeletal muscle, liver, pancreas, stomach, spleen, lymph node, bone marrow, adrenal gland, and thyroid. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of NOV21c.

Homologies to any of the above NOV21a, NOV21b and NOV21c proteins will be shared by the other NOV21 proteins insofar as they are homologous to each other as shown above. Any reference to NOV21 is assumed to refer to NOV21a, NOV21b and NOV21c proteins in general, unless otherwise noted.

NOV21a, NOV21b and NOV21c are very closely homologous as is shown in the amino acid alignment in Table 21H.

Table 21H. ClustalW of NOV21a, NOV21b and NOV21c